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PTO/SB/33 (07-05)
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PRE-APPEAL BRIEF REQUEST FOR REVIEW	Docket Number (Optional) 514162000120	
	Application Number 10/014,220	Filed November 9, 2001
	First Named Inventor Che-Kun James SHEN	
	Art Unit 1633	Examiner S. Kaushal

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant /inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☐ attorney or agent of record. Registration number _____
- ☒ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34. 48,751

Signature

Otis Littlefield
Typed or printed name

(415) 268-6846
Telephone number

June 19, 2007
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of 1 forms are submitted.

I hereby certify that this correspondence is being facsimile transmitted to the Patent and Trademark Office, facsimile no. (571) 273-8300, on the date shown below.

Dated: June 19, 2007 Signature: Valerie Cohen (Valerie Cohen)

sf-2340717

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted by facsimile to the Patent and Trademark Office, facsimile no. (571) 273-8300, on the date shown below.

Dated: June 19, 2007 Signature: Valerie Cohen
(Valerie Cohen)

Docket No.: 514162000120
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Che-Kun James SHEN

Application No.: 10/014,220 Confirmation No.: 5165

Filed: November 9, 2001 Art Unit: 1633

For: HS-40 ENHANCER-CONTAINING VECTOR IN TRANGENIC ANIMALS Examiner: S. Kaushal

ARGUMENTS ACCOMPANYING PRE-APPEAL BRIEF REQUEST FOR REVIEW

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The following arguments are presented in support of the Pre-appeal Brief Request for Review being filed concurrently with a Notice of Appeal.

sf-2253067

ARGUMENTS

1. New Matter Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has maintained the rejection of Claims 21-34 under 35 U.S.C. § 112, first paragraph, alleging that the amendment filed on 8/01/05 as modified by the amendment filed on 9/27/06 introduces new matter into the disclosure, and that the recitation "integrated" in claim 21 is not supported by the original disclosure. (Office Action, page 2). Applicant respectfully traverses the rejection and the supporting remarks. Claim 21 recites "an animal cell whose genomic DNA comprises at least one copy of an integrated transgene comprising ..." Applicant has cited to paragraph [0004] of the specification in support of the claimed transgene being an integrated transgene.

> Gene expression in transgenic animals ***is often limited by the position in the genome where the transgene is integrated*** and by the number of copies of the transgene which have integrated.

The Examiner dismissed this paragraph as a generic statement of the state of the transgenic art; however, this is simply not accurate. This paragraph is stating a problem in gene expression of integrated transgenes which is related to the position of integration. As paragraph [0006] makes clear, the invention solves this problem suffered by integrated transgenes.

> The invention is based upon the discovery that a single nucleotide change in the 3'NF-E2/AP1 element of the human HS-40 enhancer HS-40(mt), unlike the wild type enhancer, ***confers position-independent*** and copy number-dependent expression of the gene ***in the cells of transgenic animals***, an effect not seen for the wild type HS-40 enhancer.

The standard for determining compliance for the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (citations omitted)." In this case, one of skill in the art would read the background as setting forth a problem experienced with integrated transgenes (position-dependent expression) and recognize from the summary that the claimed enhancer element solves this problem experienced with integrated transgenes by providing position-independent expression. It would be absurd for one of skill in the art to read this and assume that the inventors did not invent "an animal cell whose

genomic DNA comprises at least one copy of an ***integrated*** transgene comprising ..." The invention is directed to solve a problem of integrated transgenes in animal cells, so of course the inventors invented integrated transgenes in animal cells. Thus applicant submits that the claim as currently amended complies with the written description requirement, and withdrawal of the new matter rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

Rejection under 35 U.S.C. § 102(b)

The Examiner rejected claims 21, 23-27 and 30-32 under 35 U.S.C. § 102(b) as allegedly being anticipated by the reference of Zhang *et al.* (1995) JBC 270(15):8501-8505 in view of the teachings of Ohtani *et al.* (1989) Nucleic Acids Res. 17(4):1589-604. Applicant respectfully traverses the rejection and the supporting remarks. Zhang *et al.* teach electroporation of isolated animal cells with a transgene that introduces the transgene into the cells for transient transfection assays. The cells are cultured for five days and then assayed for activity. (See 2nd full paragraph, col. 2, page 8502) In transient transfection assays, the cells are not cultured for a long enough period of time for the transgene to have integrated. The Declaration of Dr. Shen supports this where he asserts that no cells would have been stably transfected within the time period of the assay (See paragraph 4). The Examiner has asserted that even though Zhang *et al.* do not expressly teach isolated cells with an integrated transgene (because it's a transient assay), that culture of the electroplated cells for five days would inherently have resulted in at least one of the transgenes having integrated in a cell. If the transgene did not integrate, then there is no *prima facie* case because the teachings of Zhang *et al.* would lack the element of an "***integrated*** transgene." The Examiner has asserted that Ohtani *et al.* demonstrates that at least one would have inherently integrated within the five day period. However, Ohtani *et al.* only shows that after 14 days the transfected construct has integrated. The only fact that the Examiner has cited in support of integration in a period shorter than 14 days is that the cells in Ohtani *et al.* were subject to selection to isolate cells that were transfected stably at the time of transfection (Ohtani *et al.* actually teach addition of the selection beginning 2 days after transformation (see, *e.g.*, center paragraph page 1592 and top of 1596)). However, as demonstrated by Zhang *et al.*, transgenes clearly show expression five days after electroporation into the cells even though the transgenes have not yet

integrated. Thus, contrary to the Examiner's assertion, there is no need for the genes with the neo resistance marker taught by Ohtani *et al.* to have integrated in order for the cells to have survived challenge with G418 beginning two days after transformation. Thus, the Examiner has at best only established that some small number of the cells taught by Zhang *et al.* may have become integrated if the cells had been maintained for 14 days. The Examiner has not cited to any evidence in support of a single transgene having integrated into a single cell within 5 days of culture as taught by Zhang *et al*, while applicant has provided evidence in the form of a declaration that the opposite is true. Thus the Examiner has created no factual issue with regard to inherent anticipation. Therefore, applicant respectfully request that the Examiner withdraw the rejection of claims 21, 23-27 and 30-32 under 35 U.S.C. 102(b).

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected claims 21, 23-27 and 30-32, in the alternative, under 35 U.S.C. § 103(a) as allegedly being obvious over Zhang *et al.* (1995) JBC 270(15):8501-8505 in view of Ohtani *et al.* (1989) Nucleic Acids Res. 17(4):1589-604. Applicant respectfully traverses the rejection and the supporting remarks. Applicant dispute whether one of skill in the art would modify Zhang *et al.* to include the electroporation and integration of the transgene as taught by Ohtani *et al.* However, for the purpose of the Pre-Appeal Brief Conference, Applicant chooses to focus on the secondary consideration of unexpected results that fully rebuts any *prima facie* case of obviousness. Applicant has asserted that the claimed invention produces the unexpected result of position-independent expression, which the Examiner has asserted is not a feature of the pending claims. But this feature is captured by the recitation "the level of expression being positively correlated with the copy number of the transgene," *i.e.*, regardless of where the transgene integrate (position-independent) the transgene will express a relatively constant amount so that more transgenes integrating (the copy number) leads to increasing level of expression (positively correlated). This result is clearly surprising. Table 1, page 14, of the specification shows that the wild type enhancer shows wildly varying levels of expression with increasing copy number (i.e. its not positively correlated as claimed (i.e., position-dependent expression)). For example, the lines with a copy number of 5, 10 or greater than 100 (100B) show lower expression that 1A which has

only a single copy. By contrast, the mutant HS-40 transgene (SEQ ID NO:1 as is presently claimed) shows a positive correlation – higher copy number yields higher expression (i.e., position-independent expression) for every mouse obtained with the exception of one mouse – 1C. Since the wild-type enhancer sequence fails to produce the position-independent expression as is presently claimed, it is quite unexpected that claimed SEQ ID NO:1 enhancer which has only a single base pair mutation would provide the claimed effect. The Examiner has disputed whether the claimed effect is surprising by asserting that the prior art demonstrates that the HS-40 element is capable of expressing in a variety of cell types and that Walters *et al.* (1995) PNAS 92:7125-7129, teaches that enhancers provide position-independent expression. The fact that the wild type HS-40 element is functional in a variety of cell types is irrelevant as position-independent expression is not referring to type of cell, but rather where in the genome of a particular cell the transgene integrates. Further, Walters *et al.* actually support that the claimed positive correlation between expression and copy number is surprising. See, *e.g.*, top of col. 1, page 7125, "In stably transfected clones [integrated], differences in expression levels are found, but ***these are not related to either the copy number*** or the presence of an enhancer," and Figure legend 5, "Neither construct demonstrates expression that is copy number dependent." Thus Walters *et al.* observed ***no correlation*** between copy number of the transgene and expression while the presently claimed SEQ ID NO:1 results in a transgene with ***positive correlation*** between copy number and expression (i.e., position-independent expression). Thus, the Examiner has not created any factual issue of whether the claimed result is surprising and has actually provided evidence that proves how surprising the result is. Therefore, applicant respectfully request that the Examiner withdraw the rejection of claims 21, 23-27 and 30-32 under 35 U.S.C. 103(a).

Dated: June 19, 2007

Respectfully submitted,

By _____

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sf-2253067